Docket No.: 2815-0335PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bjarne H. DAHL et al.

Application No.: 10/561,189 Confirmation No.: 3923

Filed: December 16, 2005 Art Unit: 1626

For: DIPHENYLUREA DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS Examiner: S. L. Chung

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Palle Christophersen, so hereby declare the following:

I am the Vice President and Director of In Vitro Pharmacology at NeuroSearch A/S of Ballerup, Denmark.

A copy of my curriculum vitae is attached hereto.

I have read and understand the specification and claims to the above-identified application and the outstanding Office Action of July 15, 2008 (hereinafter "Office Action"), in particular the rejections over obviousness-type double patenting over Claims 1-15 of USP 6,297,261; Claims 1-13 of USP 6,696,475; Claims 12-20 of published application No. 2006/0058395 and Claims 21-39 of published application No. 2006/0160856.

Attached hereto as Exhibit A is data that shows that the compounds of the instant invention possess unexpected advantageous properties compared to the prior art compounds, as evidenced by a K_D value more than 100X lower than that of the prior art compounds. With the

attached data, Compound A is a claimed compound of the instant invention, i.e. *N*-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea. Compound B is *N*-(3,5-Dichloro-phenyl)-*N'*-[4'-carboxamid-2-(1H-tetrazol-5-yl)-4-biphenyl urea from US 2006/0160856 and the Compounds C, D and E are respectively, N-(3-Trifluoromethylphenyl)-N'-(4'-carboxy-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea; 3-Trifluoromethylphenyl-4-phenyl-2-(5-tetrazolyl)phenyl urea and 3-Trifluoromethylphenyl-4-(4-aminocarbonylphenyl)-2-(5-tetrazolyl)phenyl urea, which are all disclosed in USP 6,297,261, USP 6,696,475, and US 2006/0058395. Exhibit A further discusses the comparative study done with these compounds.

I hereby declare that all statements made herein of any own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 13-11-2008

Palle Christophersen

Palle Christophersen, PhD

Enclosures: Exhibit A: Comparative data

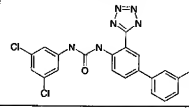
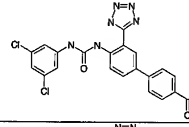
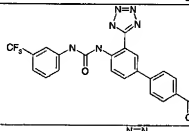
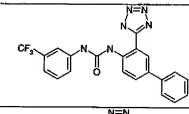
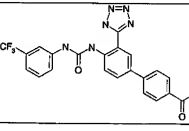
EXHIBIT A
Comparative Data

In this exhibit the effect of the compound of the invention *N*-(3,5-dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea (compound A, 4th compound on page 19 of the specification) and the prior art compounds *N*-(3,5-dichloro-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea (compound B; of WO 2004/022529) and 3-trifluoromethylphenyl-4-(4-aminocarbonylphenyl)-2-(5-tetrazolyl)phenyl urea, 3-trifluoromethylphenyl-4-phenyl-2-(5-tetrazolyl)phenyl urea, and *N*-(3-trifluoromethylphenyl)-*N'*-(4'-carboxy-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea (compounds C-E; all of US 2002-037905) on the Volume Regulated Anion Channel (VRAC) was tested by the whole cell patch clamp technique using Human Embryonic Kidney cells (HEK293) as described in Helix et al, 2003.

In short, VRAC was activated by swelling of the cell in hypotonic (75 % tonicity) extracellular salt solution and the anion current elicited by voltage ramps was measured vs. time. After stabilization of the current the compounds (A and B, respectively) were added to the extracellular solution and the time dependent block was followed for calculation of the K_D values.

The values obtained are shown in Table 1:

Table 1

Compound	Structure	K_D value
Compound A of the invention 4th compound on page 19 of the specification		0.095 μM
Compound B, 5th compound on page 45 of the specification of WO 2004/022529		> 1 μM
Compound C, 6th last compound of Example 2, right column on page 13 of the specification of US 2002/0037905		> 1 μM
Compound D, 4th compound of Example 2, right column on page 13 of US 2002-0037905		> 1 μM
Compound E, 15th compound of Example 1, right column on page 12 of US 2002-0037905		> 1 μM

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1986-1989	Ph.D. student, August Krogh Institute, Dept. B., University of Copenhagen.
1989-1991	Scientist at Center for Biomembranes, University of Århus.
1991-	Research scientist, electrophysiology, NeuroSearch A/S
1995-2002	Project manager, NeuroSearch A/S
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2004-	Director of In Vitro Pharmacology, NeuroSearch A/S
2006-	Vice President, NeuroSearch A/S

Number of publications in peer reviewed journals and books: 49
Accepted manuscripts: 2
Submitted manuscripts: 2
Number of patent publications: 61

SELECTED PUBLICATIONS

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